Buccal drug delivery technologies for patient-centred treatment of radiation-induced xerostomia (dry mouth)

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Abstract
Radiotherapy is a life-saving treatment for head and neck cancers, but almost 100% of patients develop dry mouth (xerostomia) because of radiation-induced damage to their salivary glands. Patients with xerostomia suffer symptoms that severely affect their health as well as physical, social and emotional aspects of their life. The current management of xerostomia is the application of saliva substitutes or systemic delivery of saliva-stimulating cholinergic agents, including pilocarpine, cevimeline or bethanechol tablets. It is almost impossible for substitutes to replicate all the functional and sensory facets of natural saliva. Salivary stimulants are a better treatment option than saliva substitutes as the former induce the secretion of natural saliva from undamaged glands; typically, these are the minor salivary glands. However, patients taking cholinergic agents systemically experience pharmacology-related side effects including sweating, excessive lacrimation and gastrointestinal tract distresses. Local delivery direct to the buccal mucosa has the potential to provide rapid onset of drug action, i.e. activation of minor salivary glands within the buccal mucosa, while sparing systemic drug exposure and off-target effects. This critical review of the technologies for the local delivery of saliva-stimulating agents includes oral disintegrating tablets (ODTs), oral disintegrating films, medicated chewing gums and implantable drug delivery devices. Our analysis makes a strong case for the development of ODTs for the buccal delivery of cholinergic agents: these must be patient-friendly delivery platforms with variable loading capacities that release the drug rapidly in fluid volumes typical of residual saliva in xerostomia (0.05 to 0.1 mL).

Keywords
Radiation-induced xerostomia, saliva, salivation, salivary substitutes, salivary stimulants, orally disintegrating films, orally disintegrating tablets, patient-centred, pilocarpine HCl, dry mouth, head and neck cancer.

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1 Introduction

1.1 Radiation-induced xerostomia (dry mouth)

Head and neck cancer is a general term that includes cancers of oral cavity, pharynx, nasal cavity and larynx. In the UK, the average national incidence of the head and neck cancer was 19.2 per 100,000 of the population (Cancer Research UK A), and the majority of this population is diagnosed with head and neck cancer at the age of 60 to 69 years old (Cancer Research UK B). The most commonly used treatments for patients with head and neck cancers are radiotherapy, chemotherapy, and surgery or combination of these approaches. Salivary gland damage occurs in 95% to 100% of patients treated with radiotherapy, which leads to the development of xerostomia (Chambers et al., 2004). Xerostomia is the subjective feeling of dry mouth which may exist as a consequence of reduced salivary flow (Cassolato and Turnbull, 2003). Head and Neck cancer patients not only suffer from oral distress but other clinical complications such as malnutrition, dental problems, and depression, not surprisingly, all of these compromise the quality of the patient's life (Chambers et al., 2004).

This review aims to investigate whether improvements to the formulations currently used to treat radiation-induced xerostomia are possible. The review critically evaluates the current options for the treatment of radiation-induced xerostomia and advocates local administration of saliva-stimulating agents to the buccal region. Our evaluation recognises that any product for delivering drugs to stimulate the secretion of saliva should be designed in accordance with the principles of patient-centred medicines, i.e. with patient requirements at the core of the design.

1.2 Saliva and salivation

Saliva is a very complex fluid; water forms the main fraction combined with electrolytes, minerals, buffers, growth factors, enzymes, cytokines, proteins, and immunoglobulins (Amerongen and Veerman, 2002). These components are vital in maintaining oral homoeostasis that includes good oral health, mastication, digestion, regulation of oral flora, speech and oral cleansing (Amerongen and Veerman, 2002). Saliva is produced by the major and the minor salivary glands. The major salivary glands are pairs of parotid, sublingual and submandibular salivary glands (fig 1).

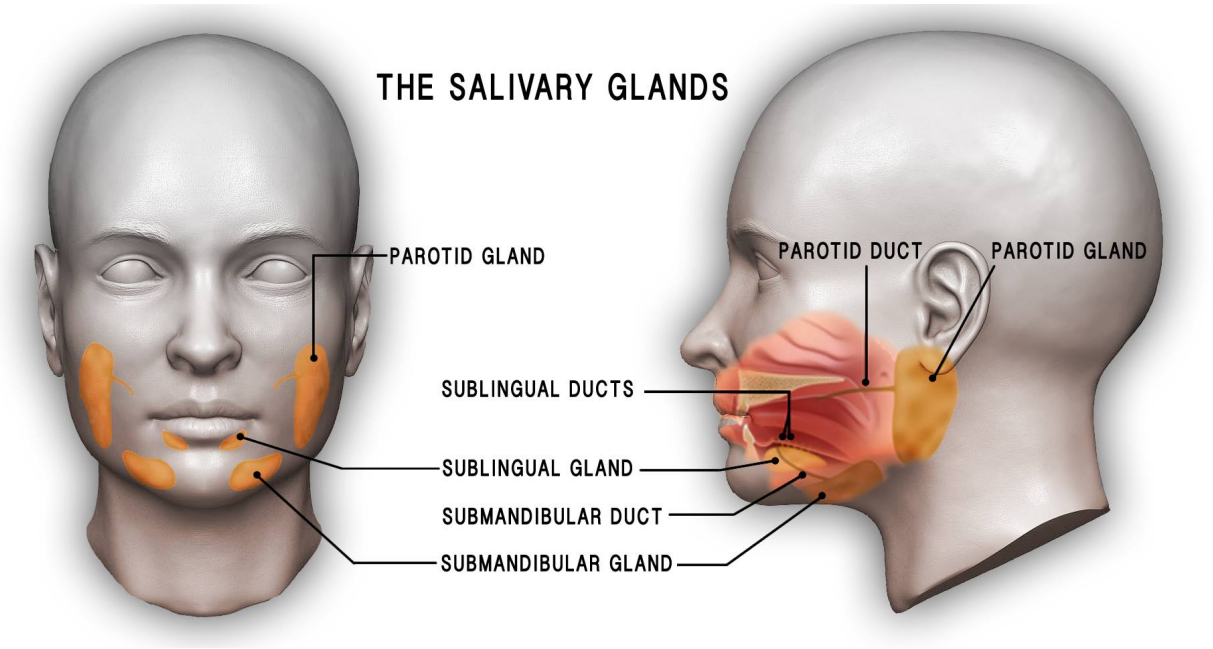

Figure 1: Illustration of salivary glands types and position.

The minor salivary glands are 600 to 1000 glands distributed throughout the oral cavity, in the sub-mucosal layer beneath the oral mucosal surface, with greatest density in the buccal cavity and lips (Dodds et al., 2005; Wang et al., 2015). Although 90% of the average daily salivary secretion, 1 to 1.5 L, is produced by major salivary glands, the minor salivary glands spontaneously produce around 10% of the total average of salivary secretions (Sonesson et al., 2003). Minor salivary glands produce salivary secretion that is rich with mucin protein which protects the oral mucosa from dryness (Sonesson et al., 2003). For the major salivary glands, the unstimulated salivary flow average is 0.3 mL/min (Amerongen and Veerman, 2002), whereas, the stimulated salivary flow rate is between 1 to 2 mL/min (Sreebny, 2000). The lowest salivary flow rate is during sleeping, (0.1 mL/min), and the maximum flow rates, 4 to 5 mL/min, are observed during mastication or stimulation (Porter et al., 2004). The minor salivary glands' flow rate varies according to the anatomical location. For example, in a study of 300 healthy subjects the mean saliva flow rates were 2.10 ± 0.66 µL/min/cm^2 (lower labial glands), 2.14 ± 0.62 µL/min/cm^2 (upper labial glands), 2.88 ± 0.72 µL/min/cm^2 (buccal glands) and 2.15 ± 0.51 µL/min/cm^2 (palatal glands), respectively (Wang et al., 2015). The flow rate of buccal glands was significantly higher than the rates of other locations ($P<0.01$) (Wang et al., 2015).

The microanatomy of both types of salivary glands is similar. Salivary gland cells are mainly acinar cells, various duct systems cell, and myoepithelial cells. In general, acinar cells determine the type of saliva secreted by different glands (Holsinger and Bui, 2007). Parotid glands produce the serous type of saliva while the mucous type of saliva is produced by the minor salivary glands and by the sublingual gland. The mixed type of saliva (serous and mucous) is generated by the submandibular salivary glands. Duct system cells act as a network to transport saliva from site of production to the oral cavity, and myoepithelial cells help in the saliva secretion proses (Holsinger and Bui, 2007).

Salivation is induced under the control of sympathetic and parasympathetic nervous system. The major salivary glands are innervated by both sympathetic and parasympathetic nervous system stimulants, while the minor salivary glands are supplied with little or no sympathetic innervations (Proctor and Carpenter, 2007). Salivary production is mediated through the binding of sympathetic and

parasympathetic neurotransmitters to their receptors. Acetylcholine is the parasympathetic neurotransmitter that binds to five subtypes the muscarinic receptors, M1-M5 (Gautam et al., 2004). Knockout gene experiments using mutant mice revealed that M1 and M3 control of salivary secretion (Gautam et al., 2004). The sympathetic nervous system activation is mediated by the binding of the sympathetic neurotransmitter, adrenaline, to alpha1- and beta1- adrenoceptors, on the surface of the acinar cells (Proctor and Carpenter, 2007).

1.3 Radiation-induced xerostomia

The standard treatment plan for patients diagnosed with head or neck cancer is radiation therapy usually combined with surgery and/or chemotherapy (Yom, 2015). The major salivary glands are more externally located with respect to most of the tumours attributed to head and neck cancer and therefore are usually present in the fields of radiation exposure (Vissink et al., 2015a). Different treatment procedures are available to treat patients with head and neck cancer. Conventional radiotherapy (RT) and intensity-modulated radiotherapy (IMRT) are among these strategies, and they affect salivary glands' hypofunction and thus affect the prevalence of xerostomia. Several studies have shown that salivary function and salivary flow rate are better preserved when using IMRT (Tribius and Bergelt, 2011). For example, patients reported less severe xerostomia when treated with IMRT in comparison to conventional RT (Michael et al., 2007). The severity of xerostomia was 39.3% vs 82.1%; P = 0.001, with higher stimulated parotid flow rate (0.90 mL/min v 0.05 mL/min; P = 0.0001), and higher stimulated whole salivary flow rate (0.41 mL/min v 0.20 mL/min; P = 0.001) (Michael et al., 2007). Standardisation of the total amount of IMRT dose fractionation for head and neck cancer is difficult, as this depends on the extent of the patient's tumour. However, a typical plan is to treat patients with a total amount of radiotherapy between 50 to 70 gray (Gy). This is achieved by a daily fraction, for example 2 Gy, over a period of many weeks (Kean et al., 2009). Common changes observed in the salivary glands after irradiation treatment are degranulation and necrosis of the acinar cells due to their membrane damage, as well as chronic inflammation and fibrosis of the gland lobules, especially in the periductal and intraocular areas (Grundmann et al., 2009; Konings et al., 2005). As a result, a rapid decrease of up to 50-60% in the salivary function in the initial phase of treatment, if the radiation passes through the major salivary glands (parotid, sublingual and submandibular). Upon completion of the treatment, saliva usually falls to its minimum flow rate (Chambers et al., 2004). In healthy individuals, the stimulated and the unstimulated salivary flow averages are 1 to 2 mL/min and 0.3 mL/min, respectively (Amerongen and Veerman, 2002; Sreebny, 2000). In contrast, individuals are considered to have xerostomia when the unstimulated flow rates are less than 0.1 mL/min and when the stimulated salivary flow rates are less than 0.5 mL/min (Humphrey and Williamson, 2001).

Studies of radiation-induced xerostomia that consider the impact of radiation on minor salivary glands are scarce (Pinna et al., 2015). However, in comparison to major salivary glands, the minor salivary glands are less sensitive to radiation since serous cells are more susceptible to radiation damage than the mucous cells (Van de Water et al., 2009). Additionally, minor salivary glands are higher in number and are more widely distributed (Dodds et al., 2005).

Radiotherapy not only reduces salivary flow but it also induces changes in the chemical composition of the saliva. Studies have shown a statistically significant change in the saliva electrolyte concentrations during the development of radiation-induced xerostomia. For example, there are noted concentration increases in sodium, calcium, magnesium and chloride ion (table 1) which are all dependent on salivary flow rate (Pinna et al., 2015). Radiation treatment also contributes to a decrease in saliva bicarbonate concentration, and this affects buffer capacity. These changes are related to damage to the secretory

units and tubules of the salivary glands. As a result these alterations and in addition to a reduction in water content, the saliva becomes very viscous and acidic with a change in pH from 7 to 5 (Pinna et al., 2015).

Table 1: The concentration of saliva components before and after radiation treatment. Table adapted from (Dreizen et al., 1976), a study carried out with samples of stimulated whole saliva of 30 patients with head or neck tumours. This table also includes the result of the analysis of 39 patients who were diagnosed with nasopharyngeal carcinoma, (Pow et al., 2016). Data collection points were every 3, 6 and 12 months. The table illustrates the six months' data average. Based on the concentrations of the saliva components listed below, the estimated salivary ionic strength before and after radiotherapy is 88 mmol and 148 mmol respectively. P or probability level of less than 0.001 indicates statistically significant changes in the measurements.

Saliva components	*Before Radiotherapy (mEq/L)*	*After Radiotherapy (mEq/L)*	*P value*
Sodium (Na^+)	38.42	78.27	<0.001
Calcium (Ca^{2+})	1.51	2.80	>0.05
Magnesium (Mg^{2+})	0.37	0.99	< 0.001
Chloride (Cl^-)	24.68	45.03	< 0.001
Bicarbonate (HCO_3^-)	19.80	7.95	< 0.001
Nitrate (NO_3^-)	0.21	0.06	0.015
Sulphate (SO_4^{2-})	0.10	0.22	< 0.001
Lactate ($C_3H_6O_3^-$)	0.01	0.15	< 0.001
Formate (CHO_2^-)	0.01	0.04	0.011
Propionate ($C_3H_6O_2^-$)	0.05	0.06	Unknown
Acetate ($C_2H_3O_2^-$)	0.54	0.59	Unknown
Thiocyanate (SCN^-)	0.30	0.06	< 0.001

1.4 Impact of xerostomia on health and quality of life

Abnormalities which affect the quality or quantity of saliva will diminish the quality of life of patients. The quality of life is defined as "*the assessment of an individual's well-being, including all emotional, social and physical aspects*" (Dirix et al., 2008). Oral cavity dryness, inflammations, and ulcers start to appear at the early stages of xerostomia, which translates into difficulties in speech and swallowing. Difficulties in speaking affect patients' ability to communicate and work. Moreover, any change in the saliva quality will lead to a reduction in the number of taste buds (Henkin et al., 1972). Thus, patients with xerostomia will experience a reduction of nutritional intake that will lead to significant weight loss in many patients (Chencharick and Mossman, 1983). Microbial infections and dental caries develop because of the loss of antimicrobial and antifungal properties of saliva (Gurkar et al., 2016). Reduction in saliva production causes a thirstiness sensation that affects the patient's sleep patterns as they need to moisturise the mouth constantly. To alleviate the symptoms, patient's take regular sips of liquid which results in the significant production of urine that further disturb sleep patterns. Thus, the impact of radiation-induced xerostomia on a patients' health and quality of life must be taken into consideration when designing better therapeutic products to treat this condition (section 4, page 16).

2 Current treatments for xerostomia

Commercially available treatments of radiation-induced xerostomia aim to elevate dry mouth symptoms by either using salivary substitutes when salivary glands are completely damaged or by using salivary stimulants when there is residual salivary gland function.

2.1 Salivary substitutes

Salivary substitutes, for example, water, milk and artificial saliva, are used to provide lubrication and to moisturise the oral cavity surface and therefore relieve the sensation of dryness. It has been reported that frequent sips of water are effective in dry mouth management. Moreover, using milk was also found to be beneficial as it contains chemical constituents that contribute towards lubrication, moisturising and buffering oral acid (Herod, 1994). Artificial saliva is the term given to commercial products that contain specific ingredients that mimic one or more of the properties of the natural saliva (table 2). Salivary substitutes are available in different dosage forms such as liquids, sprays and lozenges (table 2, BNF, 2016). Patients' selection of salivary substitutes is based on lubrication effect, duration of action, taste, delivery system and price of the product. The first generation of artificial liquid saliva substitutes were aqueous solutions of carboxymethylcellulose (CMC), mineral salts, fluoride, sweeteners, and preservatives that mimicked the actual saliva composition (Temmel et al., 2005). Mucin is a natural salivary protein which is responsible for protecting the oral mucosa from dryness. Therefore, the second generation of artificial saliva included mucin as an ingredient, and these were well tolerated by patients (Davies, 2000).

Table 2: Examples of currently available salivary substitutes that can be prescribed in the UK for radiation-induced xerostomia

Product name (Manufacturer)	Formulation	Composition	Application (when required)
AS Saliva Orthana® (AS Pharma) 	Oral spray 50 mL	Gastric mucin 3.5% w/v, xylitol 2% w/v, sodium fluoride 4.2 mg/L, as well as preservatives and flavoring agents. pH neutral, aqueous base formulation.	Spray onto oral and pharyngeal mucosa 2-3 times.
	30-lozenge pack	Mucin 65 mg, xylitol 59 mg in a sorbitol basis, pH neutral.	Dissolve lozenge in the mouth.
Biotène Oralbalance® (GSK) 	Mouth Gel 50g	Lactoperoxidase, Lactoferrin, lysozyme, glucose oxidase and xylitol in a gel basis, alcohol-free.	Apply directly to gingivae or tongue.
BioXtra® (RIS products) 	Mouth Gel 40 mL	Lactoperoxidase, Lactoferrin, Lysozyme, whey colostrum, xylitol and other ingredients. Alcohol-free, aqueous base formulation.	Mouth gel application when required.
Glandosane ® (Fresenius Kabi) 	Aerosol spray 50 mL	Carmellose sodium 500 mg, sorbitol 1.5 g, KCl 60 mg, NaCl 42.2 mg, $MgCl_2$ 2.6 mg, $CaCl_2$ 7.3 mg and K_2HPO_4 17.1 mg/50 g, pH 5.7, suspension.	Spray onto the oral and pharyngeal mucosa for 1-2 seconds as often as required.
Aquoral® (Sinclair IS) 	Oral Spray 40 mL	Contains oxidised glycerol triesters, silicon dioxide and flavoring agent Include aspartame, suspension.	One application to the buccal pouch, 3-4 times a day.

Owing to the biochemical complexity of natural saliva (fig 2), no salivary substitute can match all the physio-chemical parameters of it (Samarawickrama, 2002). Furthermore, the efficacy of a saliva substitute is also dependent on the guidance that is given to the patient, e.g. when to apply and what product to use. The manufacturer provides instructions for the use of each artificial saliva product and non-compliance with these instructions reduces the effectiveness of the salivary substitute. Patients should use different products based on the severity of xerostomia and the time of the day. For example, in severe xerostomia, a gel-like salivary substitute should be used overnight, whereas a more liquid substitute may be more appropriate during the day (Regelink et al., 1989). Saliva substitutes have a short duration of action and therefore require frequent re-application, which creates issues around patient adherence and increases the cost of therapy (Jensen et al., 2010). Therefore, the stimulation of natural saliva by the use of salivary stimulant agents may offer a better treatment option compared to salivary substitutes.

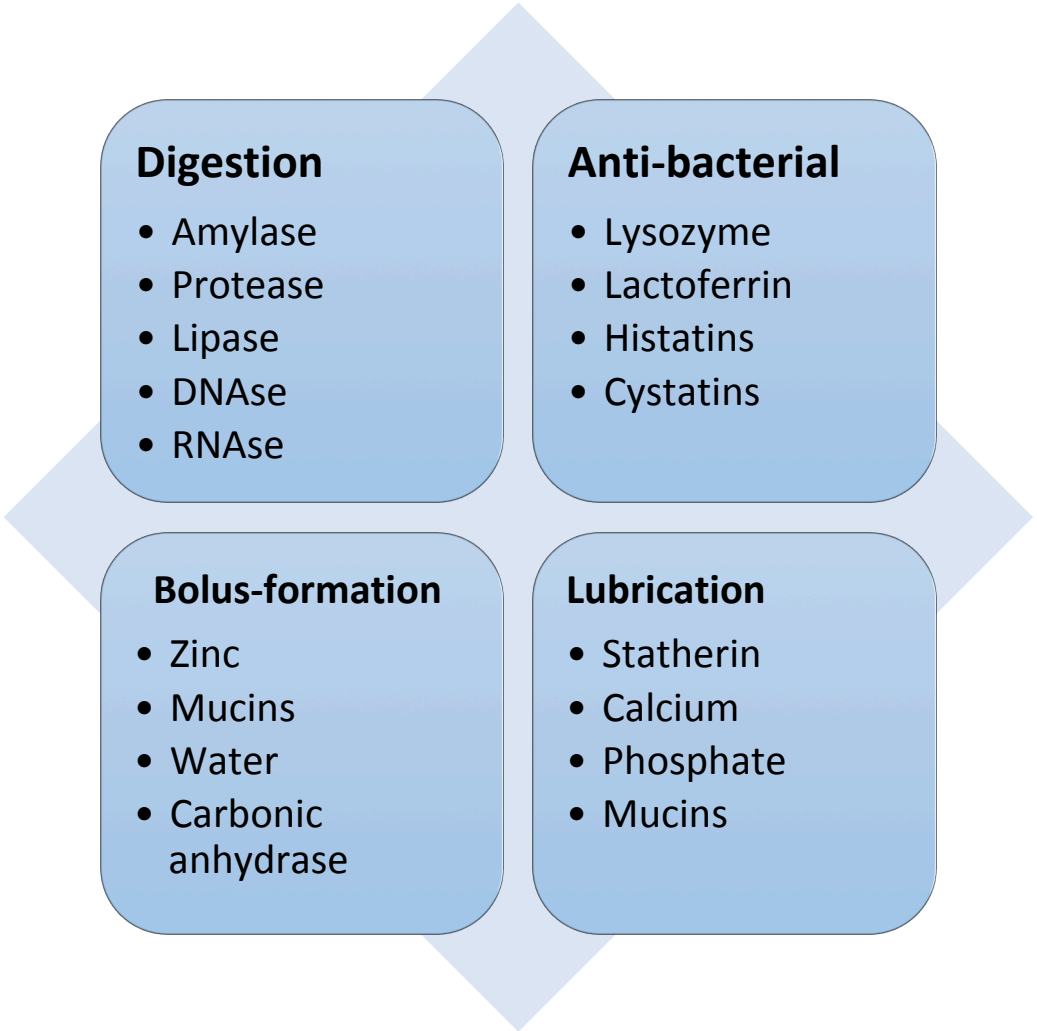

Figure 2: Examples of salivary constituents and functions.

2.2 Salivary stimulants

Cholinergic agents act through the parasympathetic nervous system and have been developed as salivary stimulants for xerostomia. These drugs, which include pilocarpine, cevimeline, and bethanechol, induce the secretion of natural saliva from the undamaged part of the salivary glands through their action on muscarinic receptors (Holmes, 1998; Napeñas et al., 2009).

Salagen® (a pilocarpine HCl tablet) is the only drug product for the treatment of radiation-induced xerostomia that has been approved in Europe and the USA. It is a film-coated tablet that contains 5 mg of pilocarpine HCl, microcrystalline cellulose as a binder, stearic acid as a lubricant and acidifier and carnauba wax as a polishing agent. Pilocarpine is effective not only in radiation-induced xerostomia but also in diseases of the salivary glands such as Sjögren's syndrome. Significant improvements to the symptoms of xerostomia can be achieved by administering 5 mg pilocarpine three times a day over a period of 8 to 12 weeks (DuRant et al., 1993). The maximum prescribed dose of 30 mg daily can be considered for patients who have not responded to the fixed dose of 5 mg three times daily (Vissink et al., 2015b). Pilocarpine can also be used as a maintenance therapy during more extended treatment periods (Acobs et al., 1996). Peak plasma concentrations of 15 and 41 μg/L for pilocarpine have been recorded after ingestion of 5 mg or 10 mg tablets three times a day, with peak concentrations reached in 75 and 50 min after administration, respectively, (Guchelaar et al., 1997). Pilocarpine is eliminated mainly in the urine with an elimination half-life of 45 and 80 min for 5 and 10 mg doses, respectively. To avoid rapid elimination and maximise exposure at the site of action, absorption of pilocarpine into the systemic system should be minimised, e.g. by local administration of lower doses direct to the undamaged salivary glands. Sublingual formulations will not fulfil this design brief as the mucosa in this region has high permeability and a generous blood supply. A buccal product that disperses and gels across the inside of the oral cavity after disintegration more closely meets the design brief.

Bethanechol is a cholinergic drug mainly used to treat urinary retention. In comparison to pilocarpine, few clinical trials have been conducted to examine the effect of bethanechol in patients with radiation-induced xerostomia (Jham et al., 2007). However, increase in salivary secretions, and improvement in dry mouth symptoms have been reported (Cotomacio et al., 2017). Cevimeline is a newer cholinergic agonist that works selectively on M3 receptors of the secretory glands, avoiding side-effects mediated by other muscarinic receptor subtypes. The efficacy and safety of 30 mg cevimeline three times a day in patients diagnosed with xerostomia as a consequence of Sjögren's syndrome has been demonstrated and cevimeline HCl tablets have been licensed by the FDA for this indication (Fife et al., 2002).

The efficacy of all the cholinergic agents described above has, to varying extent, been tested in patients with a radiation-induced xerostomia (Chambers et al., 2004). Improvements in both salivary flow rates and dry mouth sensation were reported upon using these treatments. However, pharmacology-related side-effects were reported in patients receiving all of these medications, including transient sweating, flushing or warmth, increased urinary frequency, nasal secretion, lacrimation and gastrointestinal tract distress (Chambers et al., 2004; Wiseman, 1995). Formulation of these drugs for local delivery has been advocated previously as a means of avoiding the side effects associated with oral administration (Cooper et al., 2015). The feasibility of reformulating bethanechol has been investigated by introducing a saturated solution of the drug within the buccal cavity for a fixed period to test for salivary gland activation. The initial results were encouraging, but issues concerning the physical and chemical stability of the saturated solutions must be resolved for this apparently simple formulation approach to succeed (Cotomacio et al., 2017). Although pilocarpine, cevimeline and bethanechol are all candidates for localised salivary stimulation therapy for radiation-induced xerostomia (Mercadante et al., 2017),

cevimeline is licensed by the FDA only for the treatment of xerostomia related to Sjögren's syndrome and is not available in many countries (José-Antonio et al., 2016). In contrast, pilocarpine is indicated for radiation-induced xerostomia and is widely available in most countries. This makes pilocarpine an obvious candidate for proof of concept investigations into the topical treatment of xerostomia, with more selective compounds such as cevimeline potentially providing even greater selectivity should this prove necessary.

Table 3: Treatments of radiation-induced xerostomia: limitations and research needs for better therapeutic options.

Therapeutic options	Salivary stimulants	Salivary substitutes
Products	Pilocarpine HCl tablets Bethanechol chloride tablets Cevimeline HCl tablets	AS Saliva Orthana® oral spray Biotène Oralbalance® gel BioXtra® gel Glandosane ® spray Aquoral® spray
Limitations	The limitations are due to the systematic exposure of the drug that produce off-target effects (side effects) via stimulation of the parasympathetic nervous system. These include transient sweating, flushing or warmth, increased urinary frequency, nasal secretion, lacrimation and gastrointestinal tract distress.	Short duration of action and therefore require frequent administration. The available products are simple and do not mimic the complexity of the natural saliva.
Research needs	Reformulate the products to achieve local therapeutic effect by local activation of the minor salivary glands.	Design of a product that better mimics natural saliva. Longer acting salivary substitutes are also required.

A localised buccal delivery system for pilocarpine may overcome the limitations associated with current therapy (table 3). Despite the efficacy of pilocarpine in treating radiation-induced xerostomia (table 4), its off-target cholinergic effects limit its use. Participants in clinical trials invariably reported side effects after oral pilocarpine treatment. The side effect profile reduces the willingness of patients to take pilocarpine and may result in treatment cessation. Furthermore, the parasympathomimetic activity of pilocarpine leads to concerns regarding cardiovascular effects, although no significant responses in the heart rate or blood pressure have been noted. However, its administration is contraindicated in patients suffering from hypertension or other cardiovascular or gastrointestinal illnesses (Gornitsky et al., 2004).

Table 4: Studies that investigate the efficacy of pilocarpine in patients with radiation-induced xerostomia.

Authors	Study type	Duration of the study	Treatment	Evaluation	Outcomes
Leveque et al., 1995	A double-blind study, n=207.	12 weeks	Pilocarpine 5 mg, 10 mg and placebo treatment were administrated three times a day.	Evaluation of xerostomia was based on a visual analog scale questionnaire.	The overall xerostomia was improved upon using pilocarpine HCl tablets of 5 and 10 mg dose. The over oral condition was improved in 53.5% of patients on 5mg pilocarpine, 42.9% of patients on 10 mg pilocarpine and only 25% of patients on placebo, P-value of 0.01.
Haddad and Karimi, 2002	A double-blind study, n=39.	Over the period of radiation treatment and extra three months after the end of radiotherapy treatment.	Pilocarpine 5 mg and placebo were administrated three times daily.	Evaluation of xerostomia was based on visual analogue scale questionnaire carried out six months after the end of radiation therapy.	The pilocarpine HCl tablets are more effective in comparison to placebo. Using a visual analogue scale questionnaire, the severity of subjective xerostomia was 40.5% and 57% in the pilocarpine and placebo group respectively. (P= 0:02, 95% confidence interval of the difference).
Valdez et al., 1993	A double-blind study, n=9.	12 months	Pilocarpine 5 mg or placebo were administrated four times a day.	Objective and subjective assessments were carried weekly over the first two months of the treatment and repeated later at month 3, 4, 5, 6 and 12.	Based on the objective results of the questioner, pilocarpine group reported improvements in oral dryness. During radiation therapy, a reduction of around 450 µL/min in a parotid gland flow rate was recorded in patients taking a placebo. Whereas, less than 200 µL/min reduction in parotid flow rate was registered in the group taking pilocarpine HCl tablets ($p<0.025$).
Fox et al., 1991	Double-blind study, n=39.	6 months	Pilocarpine 5 mg and placebo were administrated three times daily.	Xerostomia evaluation was based on the subjective and objective improvement that was assisted on monthly bases.	Based on the objective and subjective results, pilocarpine HCl tablets were an effective treatment for dry mouth. 90% of the patients experienced improvement in oral dryness. Unstimulated salivary flow rates of the parotid and submandibular glands were increased from, 0.003 mL/min and 0.018 mL/min to 0.048 mL/min and 0.028 mL/min respectively.

3 Design of a topical drug delivery system for salivary stimulants

Since the function of minor salivary glands is preserved better than the major salivary glands post radiation therapy, local delivery of cholinergic agents provides a means of drug targeting to the saliva-producing minor glands located just below the oral epithelium. Advantages of buccal mucosa as a site for topical drug delivery include: (i) a robust nature, this oro-mucosa has short recovery times after stress or damage (Gandhi and Robinson, 1994); (ii) the absence of Langerhans cells which offers a high level of tolerance to potential allergens (Boddé et al., 1990); and (iii) excellent accessibility and easy removal of the system in case of side effects (Lee et al., 2000). Thus drug delivery via the mucosal tissue that lines the inside of the cheeks, is an ideal approach for the localised delivery of salivary stimulants (Zhang et al., 2002). The buccal mucosa not only hosts many of the mouth's minor salivary glands, it is also a convenient route of administration (Zhang et al., 2002) and avoids the expedited drug entry into systemic circulation associated with sublingual administration (Narang and Sharma, 2011). Encouragingly, delivery of pilocarpine nitrate via the buccal mucosa in beagle dogs resulted in an absorption rate of 72.9 ± 53 μg/kg/h and an submandibular salivary flow rates of up to 0.35 mL/min (Weaver et al., 1992).

In addition to biopharmaceutical considerations, the physical, physiological and social needs of patients should be utilised in the design of a pharmaceutical drug product. This approach can maximise therapeutic benefit, enhance patient adherence and aligns with the current paradigms for the development of more patient-centred medicines (Stegemann et al., 2016).

3.1 Pharmaceutical dosage forms and technologies

A range of pharmaceutical dosage forms and technologies may be utilised to deliver pilocarpine to the buccal mucosa. These include oral disintegrating tablets (ODTs), oral disintegrating films (ODFs), chewable gums and implantable drug delivery devices. All dosage forms containing pilocarpine should disintegrate rapidly and completely in a limited amount of saliva without the need for water; e.g. in the 0.05 to 0.1 mL of saliva typically present in patients with radiation-induced xerostomia (Cho et al., 2010). The formulation should also be able to deliver pilocarpine in doses of 5 mg to 10 mg. Furthermore, all excipients and taste masking agents, (if included), must be compatible with the drug and the administered product should leave little or no solid residue (Slavkova and Breitkreutz, 2015).

3.1.1 Orally disintegrating tablets

ODTs are dosage forms which quickly dissolve, disintegrate or melt inside a patient's mouth without chewing and water intake (Moqbel et al., 2016). They have the advantages of ease of transportation and swallowing, accurate dosing, rapid onset of action and avoidance of the first pass effect (Dhagla et al., 2012). According to Fu Y et al., (2004) and Irfan et al., (2016), fast disintegrating systems should dissolve in a small amount of saliva within the maximum of 3 minutes. Currently, the accepted disintegrating times for ODTs range between 2 and 30 seconds, e.g. Xilopar Zydis® and Calpol®fastmeltsFlashtab® (Pabari et al., 2012). The pharmacopoeia guidelines provide only partial guidance on the acceptable limits for the disintegration times of ODTs and these times are typically measured using technology design for more traditional oral dosage forms (Food and Drug Adminstration, 2008). In the case of a new product designed for the delivery of cholinergic agents, salivary stimulation will be directly influenced by the disintegration time of the ODT product. Disintegration time will depend on the tablet's dimensions, weight, manufacturing technology and the method used to measure disintegration. Considering all of the possible influences, salivary stimulation in patients diagnosed with radiation-induced xerostomia should be as fast as possible, thus a rapid disintegration time is required and so a

target of 90% tablet disintegration within 10s should viewed as acceptable. Thus, pilocarpine ODT formulations should ideally include an amorphous hydrophilic polymer, such as gelatine or alginate that provides good wettability the required viscosity post-disintegration to maintain the drug on the mucus layer in addition to the structural strength of the manufactured tablet. Saccharides may also be included to provide the tablets with elegance and hardness; such sugars include mannitol and sorbitol. Mannitol especially conveys fast disintegration/dissolution when in the presence of small amount of aqueous media. Addition of saccharides also induces a more uniform pore size in ODTs prepared by freeze drying. A network of pores throughout the tablet allows the rapid water uptake. Sweeteners, pH adjusting substances and preservatives can also be included in ODTs formulations if required (Sastry et al., 2000).

A wide range of approaches and technologies are used to produce ODTs with the primary goal of a balance between short disintegrating time and good mechanical strength. Tensile strengths for ODTs have been recorded between 5 and nearly 30 N/cm^2 (Pabari et al., 2012). The most common methods for the manufacture of ODTs are freeze-drying, moulding and compression. Freeze-drying methods have the advantages of producing tablets that disintegrate rapidly, 2 to 10 s , but also are easily handled and administrated (Fu Y et al., 2004). High cost and length of processing are the main limitations for freeze-drying. However, the preparation of the feed solution to be freeze-dried is relatively straight forward as long as the API underdevelopment has a high enough water solubility. Pilocarpine HCl fulfils these criteria, as it possesses an aqueous solubility of over 100 mg/mL at room temperature. The opioid antagonist naloxone has recently been reformulated into a freeze-dried buccal tablet formed by freeze-drying. Mixtures of gelatin, mannitol and sodium bicarbonate were used to achieve disintegration times in less than 10 seconds. The relatively large fraction of gelatin, 65% w/w, did not appear to inhibit fast delivery, but it did lead to a viscous solution or gel upon disintegration, that was designed to keep naloxone in contact with the buccal mucosa and prevent it being swallowed by the patient, (Alqurshi et al., 2016). The use of gelatin and other potential gelling agents in combination with freeze-drying is a strategy that may permit both rapid disintegration and localised delivery of salivary stimulants.

Instead of beginning with an aqueous based solution, moulding and compression approaches start with the API and excipients mixed together as solid powders. Pressure is applied to these mixtures to form the desired product. However, the resulting tablets tend to be quite brittle, thus moulding and compression manufacturing methods increase the chance of breakage of the tablets during handling when the blister packaging is opened (Badgujar and Mundada, 2011). Compression methods are commonly used in pharmaceutical industry due to the low costs of production. However, compression procedures are not designed to meet the specifications for fast disintegrating tablets, such as a sufficiently high porosity of 20% or above, which is crucial for rapid disintegration (Koseki et al., 2009).

The inclusion of super disintegrants, for example, sodium starch glycolate, can improve the disintegration times for the relatively hard tablets produced by compression. For example, Nurofen® Meltlets produced by dry granulation and compression, containing 200mg of ibuprofen, disintegrate in just over 30 seconds, whereas lyophilised (freeze-dried) Zofran Zydis® ODTs with an 8 mg dose of ondansetron disintegrates in just over 2 seconds, (Pabari et al., 2012).

3.1.2 Orally disintegrating films

ODFs are dosage forms which also quickly dissolve, disintegrate or melt inside a patient's mouth without chewing and water intake (Moqbel et al., 2016). A typical ODF formulation contains in addition to the active pharmaceutical ingredient, a hydrophilic polymer, a plasticiser, a filler and a flavouring agent (Keshari et al., 2014). ODFs may contain synthetic and the natural polymers which are required to provide the ODF with excellent spreadability and good mechanical strength, (table 5).

Table 5: Examples of natural and synthetic polymers used in ODFs **(Dhagla R. et al., 2012).**

Natural polymers	Synthetic polymers
Starch	Methyl cellulose
Polymerised rosin	Hydroxypropyl cellulose
Sodium alginate	Pyrrolidone
Gelatin	

Casting (solvent and semi-solid casting), extrusion (hot melt and solid dispersion) and rolling are methods for manufacturing ODFs. Solvent casting is the most commonly used method as it is straightforward and easy. However, ODFs prepared by the solvent casting method have the disadvantages of limited production capacity, environmental concerns, and instability generated by unpredictable factors such as polymer chain relaxation, moisture absorption or loss, and polymer-plasticizer interaction during storage (Low et al., 2013). Hot-melt extrusion has the advantage of both simplicity and high production capacity and is often used to enhance the solubility of poorly soluble active ingredients (Bala et al., 2013). The complexity of equipment, elevated processing temperatures and high development costs are the main disadvantages of this method (Low et al., 2013). Finally, the rolling process is also one of the standard methods used to produce a uniform formulation matrix and a controllable thickness of film by the use of an applicator roller (Nagaraju et al., 2013). Pilocarpine has been fabricated as a sublingual film and proven effective for the treatment of Sjögren's syndrome (Rodríguez-Pulido et al., 2017), but has not been evaluated in radiation-induced xerostomia.

3.1.3 Medicated chewing gum

Medicated chewing gum is a drug delivery system containing a masticatory gum base with one or more pharmacologically active substances that can be released after a short time of mastication (Aslani and Rostami, 2015). Chewing gum delivery systems have a broad range of advantages and few side effects. The active ingredient can be delivered to induce either local or systemic effect, fast onset of action, superior taste and ease of administration without a need of water (Morjaria et al., 2004; Pratik et al., 2011). Moreover, medicated chewing gum has been successfully used to deliver a broad range of active ingredients such as nicotine, dimenhydrinate , and commercial dental products containing fluoride and carbamide (Mehring and Waukesha, 1997; Valoti. et al., 2003). Therefore, it would be interesting to reformulate pilocarpine to locally activate the minor salivary glands through direct absorption of the drug into the buccal mucosal tissues from a gum base.

For successful medicated chewing gum, the manufacturing method should be able to deliver 5 mg of pilocarpine without the need of water and with a pleasant mouth feel. The manufactured chewing gum should be stable towards humidity and temperature changes. Water soluble and water-insoluble gum bases are the typical composition of a medicated chewing gum, (table 6). There are two types of manufacturing methods available for manufacturing medicated chewing gums namely, the traditional method based on melting and a more recent direct compression approach (Maggi et al., 2005). The

direct compression method has advantages of high loading capacity, chemical stability and faster drug release (Maggi et al., 2005).

The drug release times from of medicated chewing gum are not specified by any pharmacopoeia as it is affected by many different factors. For example, the aqueous solubility of the drug influences the release rate, as the gum must be hydrated by saliva for the drug to dissolve and then diffuse through the action of chewing (Maggi et al., 2005). Moreover, the drug release from the chewing gum is also controlled by the contact time, chewing time, intensity and rate, which can vary between patients. The European Pharmacopeia suggested that 60 chews/min is the average rate to release an active ingredient from a gum (Pharmacopia, 2005). More generally, patients with dry mouth may struggle to use a chewing gum, with the crushing of the gum's initially un-wetted and hard structure causing difficulties. The absence of normal salivary flow and limited lubrication for this process will result in poor sensory mouthfeel.

Table 6: Typical component of medicated chewing gum along with their formulation percentage, functions and examples (Aslani and Rostami, 2015).

Typical components of medicated chewing gum			
Water soluble components			
Component	Proportion by weigh	Function	Examples
Sugar sweeteners	30-60%	Taste improvement.	Sucrose, dextrose, maltose, fructose.
Softener (plasticizers)	0.5-15%	Texture modification.	Glycerin, lecithin, sorbitol.
Emulsifier	15-45%	Facilitate the dispersion of two immiscible products.	Stearyl acetate, lactylic esters.
Water Insoluble gum base			
Elastomers	15-45%	Provide gum with rubbery texture.	Polyisobutylene, isobutylene.
Rubber	15%	Softener and binding agent.	Glycerol esters, terpene resins.
Filler	50%	Texture modifiers.	Magnesium and calcium carbonate.

3.1.4 Implantable drug delivery devices

Another pharmaceutical solution is to build an oral device and implant this into a prosthetic tooth crown or embed inside a denture. All implantables aim to reduce the frequency of drug administration, and in doing so such devices permit site-specific drug administration and continual release of a therapeutic agent (Scholz et al., 2008). Drug release from implantable drug delivery systems may achieve both local and prolonged drug release. Thus controlled release implants enhance the efficacy of the therapy, decrease dose-related side effects and thus improve patient's adherence because the administrated active ingredient can in some cases be individually adjusted (Scholz et al., 2008).

Implantable drug delivery devices must meet the following specific requirements to be successful: The device should be biocompatible; it must be stable and withstand the harsh environment inside the mouth, such as high humidity, temperature variations, the force of mastication and salivary buffers. Additionally, ease of manufacturing and relatively low product costs are important.

Implantable drug delivery technologies may be divided into non-degradable and degradable implant systems (Rajgor et al., 2011). The non-degradable systems include polymeric matrices reservoir-type devices and magnetically controlled platforms. The biodegradable systems have the advantage of using inert polymers that are eventually absorbed by the body. Thus, the design and development of such systems are more complicated in comparison to the non-biodegradable systems. Designing a reservoir containing pilocarpine and implanting this into a prosthetic tooth crown or inside a denture is an efficient way for the drug to be in close contact with the buccal mucosa but as yet no suitable prototype exists.

Implantable systems may also contain small electrodes that function to stimulate salivary flow. Smidt and Andy, 2010 evaluated the efficacy of an electro-stimulation device as a fixed implant for salivary secretion. The main purpose of their approach was to stimulate the secretion of natural saliva over an extended period using the implanted electrodes. This was accomplished by electrical stimulation of the long buccal nerve and lingual nerve, through an artificial dental implant. The price of such devices is expected to be high and thus will not be an option for all patients. Furthermore, this class of device requires regular maintenance as it contains a battery that needs to be replaced, microprocessors and sensors which all require removal of the implant if they fail.

4 Patient centric pharmaceutical drug product design

Consideration of the patient-medicine interface is essential during the design of any pharmaceutical formulation where the patient's needs are at the core of the design. Therefore, improvements in the delivery of salivary stimulants must be designed based on the information available regarding the needs of patients with radiation-induced xerostomia. From a patient perspective, xerostomia can make swallowing conventional tablets difficult which may lead to choking (Kaur et al., 2011). A topical buccal therapy would avoid the need to swallow a tablet.

Orally disintegrating formulations, medicated chewing gums and implantable drug delivery devices have many advantages over the conventional pilocarpine HCl tablets (table 7). However, the implantable drug delivery devices are expensive and poorly responsive to a sudden change in the patient's needs for example when eating a meal. In addition, most of the patients with radiation-induced xerostomia have dental decay and mucosal sensitivity (Murphy et al., 2007). Therefore, attaching an implant within the mouth may be problematic as decay leads to an unstable dental architecture and patients' increased sensitivity to foreign objects will reduce adherence. For medicated chewing gum, saliva is required to initiate the chewing process, and this is impossible for patients with severe xerostomia. In addition to

this, the age of patients diagnosed with head and neck cancer fall within the range of 60 to 69 years old when tooth loss is highly possible making extended chewing difficult (Liu et al., 2016).

Table 7: Shows the recommended pharmaceutical dosage forms and their attributes to improve the efficacy and patient's compliance for the conventional pilocarpine HCl tablets.

Recommended dosage forms	Attributes				
	Loading capacity	Fast delivery (90 % of the drug disintegrated within 10s)	Administered with little or no water	Local delivery	Economic
Oral disintegrating tablets	✓	✓	✓	✓	✓
Chewing gum	✓	X	X	✓	✓
Implantable drug delivery devices	✓	X	✓	✓	X
Conventional pilocarpine HCl tablets	✓	X	X	X	✓

Among the limitations of all dosage forms that are designed to release their drug in the oral cavity is the possibility that the patients may accidentally swallow these medicines before they are fully dispersed and the drug is released. However, this issue may be addressed by achieving extremely rapid disintegration of the formulation or using specific excipients to keep the drug located on the surface of the buccal mucosa. Orally disintegrated tablets quickly disintegrate with minimal effort and without the need of water, therefore, this dosage form perfectly suits elderly patients diagnosed with radiation-induced xerostomia where dysphagia is one of the most common symptoms of the condition. A study conducted by Liu et al., (2016) found that elderly people with dysphagia prefer orally disintegrating tablets over other pharmaceutical dosage forms such as chewing gums, mini tablets and dispersible tablets. Therefore, delivering the pilocarpine using an orally disintegrating tablet would be expected to enhance patient's adherence to the medicine. To achieve a patient centric design, an ODT used for the treatment of xerostomia must be optimised for shape and size. These parameters should match the dimensions of the finger print area of the thumb in order to ease administration and attachment to the buccal area. In addition, patients with radiation-induced xerostomia might require a range of therapeutic doses based on the severity of dry mouth. Freeze drying plays a central role in the development of orally disintegrating tablets whereby the dose may be easily adjusted within a known design space, to meet patient's needs by titrating different amounts of the active ingredient. Many drugs have a bitter taste so taste-masking technologies are often required in ODTs. This may be achieved by the addition of taste masking excipients to the solution prior to freeze drying, but only after compatibility with the API has been confirmed.

5 Conclusion & Recommendations

Xerostomia is common in head and neck cancer patients treated with radiotherapy. If untreated, xerostomia can cause complications including nutritional deficiencies, low mood and depression. The current treatments for radiation-induced xerostomia are suboptimal. Pilocarpine, the only pharmacophore licensed to treat this condition, is beset by off-target side effects associated with cholinergic therapy. Local application to the buccal mucosa would have the advantages of ease of administration, good bioavailability and fast onset of action. Therefore, reformulation of pilocarpine, or other salivary stimulants, as a buccal formulation would be a significant step in improved pharmacotherapy of radiation-induced xerostomia. Fast disintegrating buccal tablets containing pilocarpine could meet the needs of patients with radiation-induced xerostomia including those with dysphagia or benefitting from dose titration. Patient-centred pharmaceutical development would ensure that the technology is designed to address both the therapeutic needs and the lifestyle of those suffering xerostomia. Fragmented knowledge and uncertainties regarding target criteria for product performance can be addressed by engagement with patients and expert practitioners. Such information would help establish a design specification so that product attributes that reflect patient needs can be defined for orally dispersible pilocarpine HCl tablets.

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